

IN THE SPECIFICATION:

Please replace paragraph [0022] with the following rewritten paragraph:

[0022] The first phospholipids, with higher phase transition temperature (T_g) from 40 to ~~70~~ 74 °C, are preferably hydrogenated naturally-occurring phospholipids and saturated phospholipids with long carbon chain ($-(CH_2)_n-$, the value of n is at least 14), such as phosphatidyl choline (PC), phosphatidyl glycerol (PG), phosphatidyl serine (PS), phosphatidyl acid (PA), or phosphatidyl ethanolamine (PE). Examples of hydrogenated phosphatidyl choline (PC) are hydrogenated egg phosphatidyl choline (HEPC) ($T_g = 50\sim 55$ °C) and hydrogenated soy phosphatidyl choline (HSPC) ($T_g = 55$ °C), while examples of saturated phospholipids with long carbon chains ($-(CH_2)_n-$, the value of n is at least 14) are dipalmitoyl phosphatidyl choline (DPPC) ($T_g = 42$ °C), distearoyl phosphatidyl choline (DSPC) ($T_g = 55$ °C), diarachidoyl phosphatidyl choline ($T_g = 66$ °C), dimyristoyl phosphatidyl ethanolamine (DMPE) ($T_g = 49.5$ °C), dipalmitoyl phosphatidyl ethanolamine (DPPE) ($T_g = 64$ °C), distearoyl phosphatidyl ethanolamine (DSPE) ($T_g = 74$ °C), diarachidoyl phosphatidyl ethanolamine ($T_g = 82$ °C), dipalmitoyl phosphatidyl glycerol (DPPG) ($T_g = 41.5$ °C), distearoyl phosphatidyl glycerol ($T_g = 54.5$ °C), dimyristoyl phosphatidyl acid (DMPA) ($T_g = 50$ °C), dipalmitoyl phosphatidyl acid (DPPA) ($T_g = 66$ °C), dipalmitoyl phosphatidyl serine (DPPS) ($T_g = 54$ °C), and distearoyl phosphatidyl serine (DSPS) ($T_g = 70$ °C). The desired phospholipids may also be a combination of two or more phospholipids listed above.

Please replace paragraph [0026] with the following rewritten paragraph:

[0026] In order to prepare a paclitaxel (added amounts)/lipid molar ratio of 1/14, 1.23 mg paclitaxel was added into the alcoholic admixture of the second phospholipid-12.2 mg/ml egg phosphatidyl choline (EPC), the first phospholipid- 2.28 mg/ml hydrogenated egg phosphatidyl choline (HEPC), and other additives- 2.28 mg/ml cholesterol and 5.4 mg/ml methoxy polyethylene glycol-distearoyl phosphatidyl ethanolamine (MPEG-DSPE). In the following examples, "MPEG" represents mPEG2000-DSPE, which is regarded to have the same transition temperature as DSPE (i.e. $T_g = 74\text{ }^{\circ}\text{C}$). The alcoholic admixture may also contain other antioxidants and cholesterol or cholesterol derivatives. Examples of cholesterol derivatives include polyethylene glycol 600 mono(cholesteryl) ether sebacate and cholesteryl oleyl carbonate. Therefore, the composition of alcoholic admixture illustrated in this example was not to be limited. The solution was evaporated under vacuum to remove the solvent and form a lipid film on the wall of the round-bottom flask at which time, 1 ml, 10 % (w/v) sucrose was added to the flask for hydration. Large multilamellar liposomes were suspended, followed by sonicating for 10 mins in order to obtain small unilamellar vesicles. Paclitaxel-containing liposomes were then sterilized by filtration through 0.2 μm cellulose acetate membrane. Laser particle size analyzer (Coulter N4 plus) was used to analyze the particle sizes of the vesicles. The average diameter was approximately 120 nm. After filtration, the concentration of the incorporated paclitaxel in the liposome is determined by HPLC. It was approximately 1.0 mg/ml and the incorporation efficiency was about 80%.

Please replace paragraph [0043] with the following rewritten paragraph:

[0043] In Example 5, egg phosphatidyl choline (EPC) selected as the second phospholipid has a phase transition temperature of $-8\text{ }^{\circ}\text{C}$ which is lower than the

intravenous administration temperature (37 °C) and the storage temperature (4 °C).

Hydrogenated soy phosphatidyl choline (HSPC) selected as the first phospholipid has a phase transition temperature of 55~60 °C which is higher than the intravenous administration temperature (37 °C) and the storage temperature (4 °C); therefore, HSPC can be combined with the second phospholipid (i.e. EPC) to compose the liposomes.

Moreover, when a molar ratio of the first phospholipid (MPEG) to the second phospholipid (EPC) is 1/20, the incorporation efficiency is only 42.1% (Paclitaxel Added Amount /Lipid=7 mole%, as shown in Table 2), and the incorporation efficiency has been dropped to 67.8% and 35.4% after 14-day and 1-month storage, respectively (as shown in Table 3). However, when a molar ratio of the first phospholipid (MPEG) to the second phospholipid (EPC) is larger than 1/20, the liposomes can incorporate high content of hydrophobic drugs and remain in a stable condition. For example, when a molar ratio of the first phospholipid (HEPC/HSPC and MPEG) to the second phospholipid (EPC) is 2.5/8 (as shown in the first and fourth samples of Table 4), the incorporation efficiency has been increased to about

69.2%~82.2%, and the liposomes remain stable.

Table 4

Liposome Composition (molar ratio)						Incorporation Efficiency (%) [#]	Average Particle Size (nm)
Drug	Second Phospho- lipid	First Phospholipid		Other Additives			
Paclitaxel	EPC	HEPC	HSPC	Cholesterol	MPEG		
0.3	8	2		1	0.5	69.2	113.3
0.3	6	4		1	0.5	63.8	120.8
0.3	4	6		1	0.5	73.6	128.4
(0.3)	8		2	1	0.5	82.2	149.5
0.3	6		4	1	0.5	62.2	167.8

Incorporation Efficiency = paclitaxel incorporated in liposome / paclitaxel added amounts.

MPEG - methoxy polyethylene glycol- distearylloyl phosphatidyl ethanolamine.

Example 6

Please replace paragraph [0050] with the following rewritten paragraph:

[0050] The liposome system of the invention can be also used for incorporating other hydrophobic drugs, such as retinoic acid. To prepare a drug added amounts/lipid molar ratio of 1/3, 2 mg all-*trans* retinoic acid (ATRA) was added into the alcoholic admixture of 12.2 mg/ml egg phosphatidyl choline (EPC), 2.28 mg/ml hydrogenated soy phosphatidyl choline (HSPC), 2.28 mg/ml cholesterol, and 5.4 mg/ml methoxy polyethylene glycol-distearloyl phosphatidyl ethanolamine (MPEG-DSPE). The alcoholic admixture may

also contain other antioxidants or cholesterol derivatives. Examples of cholesterol derivatives include polyethylene glycol 600 mono(cholesteryl) ether sebacate and cholesteryl oleyl carbonate. Therefore, the composition of alcoholic admixture of this example is used for illustrating sense, rather in a restricted sense. The solution containing ATRA was evaporated under vacuum to remove solvent, and a lipid film was formed on the wall of the round-bottom flask. After evaporation, the lipid film was hydrated with 1 ml, 10 % (w/v) of sucrose to produce suspensions of multilamellar vesicles. Then, the liposome suspension was sonicated for 10 mins to obtain smaller unilamellar vesicles. Retonic acid-containing liposomes then were sterilized by filtration through 0.2 μ m CA-membrane. Particle size was analyzed by laser particle size analyzer, and the average diameter was approximately 160 nm. After filtration, the concentration of retinoic acid incorporated in liposomes was determined by HPLC, and was approximately 1.9 mg/ml. The incorporation efficiency was more than 90 %, and ATRA/lipid ratio was up to 33 mole%.

Please replace paragraph [0051] with the following rewritten paragraph:

[0051] The liposomes, prepared by the procedure described above, can also encapsulate large amounts of ATRA. Accordingly, the liposomes prepared by description of example is able to encapsulate all of retinoic acid and its derivatives. Examples of the retinoic acid derivatives include retinol, retinyl acylate and retinyl acetate. A drug/lipid ratio range for incorporation of retinoic acid and its derivatives is 1 mole%~40 mole%, and people who skill in the art are able to use and make the same.

Example 10

Please replace paragraph [0054] with the following rewritten paragraph:

[0054] The liposomes, prepared by the procedure described above, can incorporate large amounts of camptothecin. Accordingly, people who skill in the art are able to know that the liposomes system prepared by description of example should be able to incorporate all of camptothecin derivative, and a drug/lipid ratio for incorporation of camptothecin and its derivatives is 1 mole%~40 mole%. Examples of camptothecin derivative include irinotecan, topotecan, SN-38, 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxcamptothecin, 9-amino-10,11-methylenedioxcamptothecin, 9-chloro-10,11-methylenedioxcamptothecin, 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin and 7-(2-N-isopropylamino)ethyl)-(20S)-camptothecin.

Please replace paragraph [0055] with the following rewritten paragraph:

[0055] Examples 1, 2, 9 and 10 have indicated that the liposomes prepared according to the invention can incorporate large amounts of paclitaxel and its derivative, retinoic acid and its derivative, and camptothecin and its derivative. In accordance with this aspect of the invention, the liposomes, which are not limited to incorporate the compounds listed above, are capable of incorporating large amounts of paclitaxel and its derivative, retinoic acid and its derivative, camptothecin and its derivative, and mixture of combining two or more compounds listed above. Example of derivative of paclitaxel includes docetaxel. Examples of derivatives of retinoic acid include retinol, retinyl acylate and retinyl acetate.

Examples of derivatives of camptothecin include irinotecan, topotecan, SN-38, 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxcamptothecin, 9-amino-10,11-methylenedioxcamptothecin, 9-chloro-10,11-methylenedioxcamptothecin, 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin and 7-(2-N-isopropylamino)ethyl)-(20S)-camptothecin.

Example 11